

AN AMERICAN CENTURY OF BIOLOGY

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Thomas Hunt Morgan

Theodosius Dobzhansky

Hermann Muller

Alfred Sturtevant

Calvin Bridges

Francis Ryan

Edward Lewis

Joshua Lederberg

George Beadle

Edward Tatum

Salvatore Luria

Max Delbrück

James Watson

Thomas Hunt Morgan's intellectual genealogy. Scientists whose achievements are featured in this essay are highlighted.

From both a geographic and sociological perspective, the biology of the nineteenth century was much like that of previous eras. The major ideas emanated from Europe, stimulated by experiments carried out at the great British and Continental universities. The three major biological insights that dominated the thinking of biologists at the end of the nineteenth century—the insights into evolution, heredity, and development—all reflected Europe's continued preeminence in biology.

But the unifying principle underlying these three areas of inquiry was not to be discovered by the biologists of the Old World, but by the biologists of the new. Morgan's discovery that the gene was the unit of Mendel's inheritance, that it was the fuel for Darwin's evolution, and that it served as the control switch for development inaugurated an American Century in biology that accompanied the emergence of the American research university and with it the assumption of American leadership in all areas of science. Much as Thomas Hunt Morgan at

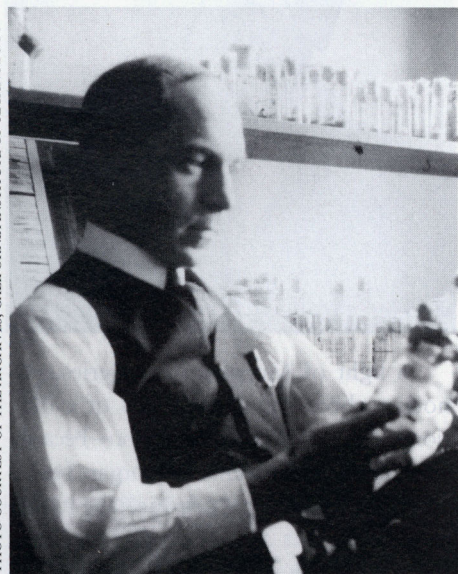
Columbia was defining and localizing the gene and thereby founding the twentieth century science of genetics, American physicists were measuring the speed of light and the charge on the electron, and American engineers were putting an aircraft in the sky.

The influence of Morgan's work at Columbia set the agenda for the decades to come, helping the American university system to establish, through its combination of teaching and research, the model for modern scientific work. Not only was Morgan the first native-born American to be awarded the Nobel Prize in Medicine or Physiology; the honor he received in 1933 for his pioneering discoveries at Columbia opened a floodgate. Over the next sixty years, some fifty Nobel Prizes in Physiology or Medicine were awarded to Americans, including several who had worked directly with Morgan or with one of his students.

The following profiles highlight the accomplishments of a core group of scientists responsible for carrying Morgan's legacy into the present.

X-ray Mutagenesis: Hermann J. Muller

One of the great strengths of genetics is its ability to identify new mutations and to study their effects on an animal during development, behavior, or learning. This



endeavor requires more than the spontaneous appearance of an occasional mutation, as Morgan had to rely on, but the ability to generate many mutations, almost at will. Credit for developing the first method of inducing *controlled evolution* goes to Hermann Joseph Muller '10C '11 '16GSAS, one of Morgan's early students at Columbia. In 1926, Muller obtained the startling result that by bombarding flies with X rays he could produce several hundred fly mutants in one day, as compared to the 400 spontaneous viable mutations that Morgan and his group had observed in working with twenty million flies during twenty years of *Drosophila* research. For his work on X-ray mutagenesis, Muller was awarded the Nobel Prize in 1946.

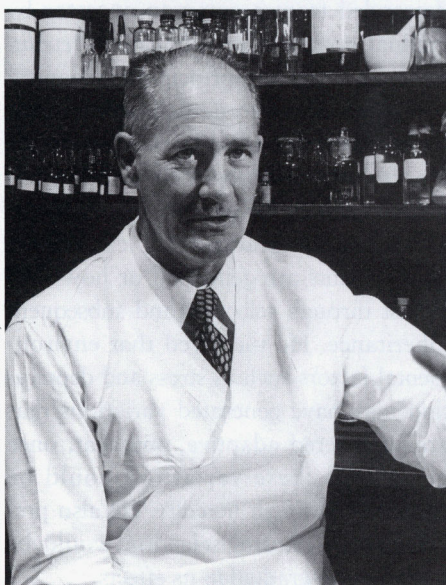
Among his other accomplishments, Muller also had the remarkable foresight to recognize as early as 1921 that microorganisms and, specifically, bacterial viruses (*phages*) offered the next step in

efforts to understand the molecular nature of the gene. It was his presence at Indiana University in the late 1940s that drew James Watson there for graduate study—though Watson ended up working with former Columbia faculty member and Nobel laureate Salvador Luria, who provided the introduction to bacterial viruses that inspired the younger scientist in his collaboration with Francis Crick to solve the chemical structure of genes.

One Gene, One Enzyme: George Beadle

Once the ability to mutate genes at will was at hand, geneticists were in a position to study how a single gene controls the function of the cell. Taking the lead in this effort was Morgan's last graduate student, George Beadle, who together with Edward L. Tatum realized in the 1940s that genes directed the manufacture of specific proteins. They subsequently introduced the concept of one gene = one enzyme.

Beadle initially focused on the genes that control eye pigment formation in the *Drosophila*, working with Boris Ephrussi in Paris to reveal that eye color is produced by a stepwise series of chemical reactions, each of which appears to be



controlled by a certain gene. Recognizing that *Drosophila* was not the ideal organism for trying to dissect multistep processes, he subsequently teamed up with Tatum and turned to a simpler, single organism, the bread mold *Neurospora*. Using Muller's method of inducing mutations with X rays, Beadle and Tatum analyzed the metabolic variations that came from these mutations and found that when a specific gene was active, the cell could synthesize a given substance; when the gene was altered or eliminated by mutation, however, the particular metabolic step at which that enzyme operated was defective, and the whole biosynthetic pathway would be slowed or brought to a stop. Their conclusion that enzymes controlled the specific stages of multi-step metabolic pathways provided direct support for an idea expressed at the beginning of the twentieth century by Scottish physician Archibald Garrod. Beadle and Tatum's hypothesis has since been refined as the one-gene-one polypeptide hypothesis, but at mid-century it represented a startling breakthrough in physiological genetics, winning the two—along with Joshua Lederberg '44C—a Nobel Prize in 1958.

Genes and the Body Plan: E.B. Lewis

The discovery that genetics could be used to analyze a biological pathway prompted an awareness that some of the most interesting pathways were related to development, raising important new questions about the way genes control developmental programs and the plan of the body. Among the leaders in exploring this new area of inquiry was Edward B. Lewis, one of Calvin Bridges' students and thus an heir to the intellectual legacy of Thomas Hunt Morgan.

Beginning in 1946, Lewis brought renewed attention to the study of homeotic mutations, which had been identified in 1915 by Calvin Bridges

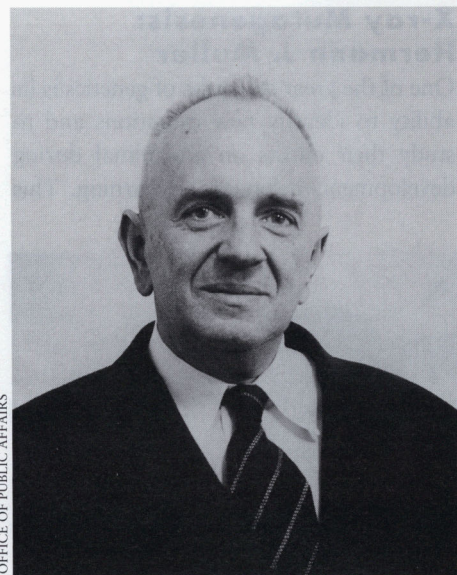
'12C '16GSAS, one of Morgan's early students. The subjects of Bridges' research included a fly that had undergone a mutation to produce an extra set of wings in place of a pair of balancers (small, winglike appendages). Bridges called the mutation "homeotic" because it changed one body part into another. This transformation—along with another homeotic mutation in a gene called *Antennapedia*—that caused legs to sprout from a fly's head where antennae would normally be—was interesting because it suggested the existence of control genes

proved to be remarkably conserved throughout evolution. Lewis further demonstrated that each part of the body is specified by different sets of active *Bithorax* genes, paving the way to an awareness that a combinatorial code defines developmental pathways. Gary Struhl, now at Columbia, subsequently split the complex to show that the individual components also work in physical isolation from one another.

Lewis's work, together with large-scale screens of *Drosophila* larvae by Eric Wieschaus and Christiane Nüsslein-Volhard, transformed development into a molecular science. For this achievement, the three were awarded the Nobel Prize in 1995.

A New Evolutionary Synthesis: Theodosius Dobzhansky

It was Morgan's postdoctoral fellow, Theodosius Dobzhansky '64HON, who first appreciated what the new genetics meant for the theory of evolution set forth in *On the Origin of Species* in 1859. Darwin, whose book had been published seven years before Mendel's report on his work with peas, spelled out two major ideas: that all organisms have descended from a common ancestor by gradual, continuous modifications (*evolution*), and that the principal mechanism of evolution is the natural selection of heritable variations. However, because he worked in the absence of information about genes and mutations, Darwin lacked any mechanism for explaining how variants are generated or how they persist through selection and subsequent inheritance. He theorized that environmental factors such as stress and deprivation may have generated variations that are considered adaptive, and that, once generated, these variations could be passed on through heredity. He also presumed that natural selection would be uniform and gradual in its effects.



OFFICE OF PUBLIC AFFAIRS

In light of Morgan's discoveries, the notion about the gradualness of evolution—long a point of contention—became even more controversial. Morgan found not continuity and gradualism in his mutations, but a level of discontinuity that he initially interpreted as a challenge to Darwin's ideas. Moreover, biologists defined a species as a form that differed in morphology from another species, and such morphological differences required major discontinuous changes.

The crucial insight offered by Dobzhansky in collaboration with Ernst Mayr was that, although a trait such as eye color could be changed by a single mutation, the majority of mutations were more gentle, or passive; over the long haul, a species would acquire a great many genetic changes, allowing for graded variations in appearance (*phenotype*) between individuals. During hard times, evolution would select for the more favorable variants, and the less favorable would be lost.

In short, genes and their various allelic forms could be seen as fueling the engine of evolution. This view reflected an influential modern synthesis in evolutionary thought first described by Dobzhansky in his classic 1937 study, *Genetics and*



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responsible for directing the development of large parts of the body.

In his work spanning five decades, Lewis built up the insight that genes control body territories, encoding the information necessary to set up each segment. His discoveries included the observation that a mutation to the members of a gene family known as the *Bithorax*-complex had led to the duplication of an entire body segment in *Drosophila*, thereby producing the extra pair of wings. He subsequently found that genes were arranged in the same order on the chromosomes as the body segments they controlled—a correspondence that has

the Origin of Species. His accomplishment in the book was to bring together the contributions of genetics, systematics, and paleontology, forging them into a neo-Darwinian theory that reconciled Darwin's original theory with the new field of genetics.

Sex and Genes in Bacteria: Joshua Lederberg

In 1944, when Joshua Lederberg was a twenty-year-old student at Columbia, he imagined that two bacteria could mate by fusing and pooling their entire genetic resources. Using a variety of genetic crosses in a highly creative way, he went on to show that this actually occurred, and that bacteria exchanged chromosomes. He



further observed that bacteria had a linear chromosome that could be mapped, establishing them as having genetics comparable to that of higher organisms.

Working with Ed Tatum, Lederberg demonstrated that the exchange of genes that sometimes took place in bacteria achieved the mix that is the evolutionary function of sex in higher organisms. Proof of such genetic recombination—which Lederberg termed *conjugation*—

had been sought before, but with no success. In 1951, Lederberg and Norton Zinder, his graduate student at the University of Wisconsin, discovered a second process, *transduction*, whereby phage particles were shown to be capable of carrying a few genes from a host into another target cell. Transduction offered the possibility of deliberately inserting known genes into a target cell, where they would function as part of that cell's chromosome. For this work, Lederberg received the 1958 Nobel Prize, sharing the award with Tatum and Beadle—an association that confirmed his place as yet another of Thomas Hunt Morgan's intellectual heirs.

The discovery of transduction marked the beginning of genetic engineering, an idea and a methodology that have carried biology to the present. Recombinant DNA has once again revitalized the field,

making it possible to clone genes, to read their sequence, to appreciate similarities between genes in different contexts, and to manipulate genes in model organisms ranging from flies to mice. These advances in molecular biology have had far-reaching consequences for understanding biological processes, including the biology of the brain and of the mental processes that the brain mediates. In addition, genetic engineering has introduced the concept of molecular medicine, with its promise of diagnosing diseases at the level of DNA—a crucial first step toward the goal of one day being able to replace defective genes with normally functioning ones.

I have benefited from the comments on this essay by Garland Allen, Norman Horowitz, Joshua Lederberg, E.B. Lewis, and Andrew Tomlinson.

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